21st Century Cures Act Regenerative Medicine Provisions: Assessing Progress Over the Last Five Years

January 2022

Alliance for Cell Therapy Now

Advancing Regenerative Medicine and Cell Therapies for Patients in Need

Executive Summary

Five years ago, Congress passed—nearly unanimously—and President Obama signed into law, the 21st Century Cures Act (P.L. 114-255), bringing historic investments to the National Institutes of Health (NIH)—$4.8 billion over ten years—and new authorities for the Food and Drug Administration (FDA).

Several sections of the law related to regenerative medicine, including provisions authorizing $30 million in funding for clinical research using adult stem cells, a new regenerative medicine regulatory framework, and guidance for industry related to the use of devices for regenerative medicine therapies.

The Alliance for Cell Therapy Now and the Alliance for Cell Therapy Foundation have examined implementation of the legislation and the status of regenerative medicine, including cell and tissue-based therapies (RMCTs), and it is clear—five years later—that the field is in a better place because of passage of the 21st Century Cures Act.

Advancements in the Field Since Passage of the 21st Century Cures Act

- As of December 31, 2021, there are more than 900 active clinical trials in the United States exploring the use of RMCTs to treat a wide range of conditions, including cancer, cardiovascular disease, diabetes, eye-related conditions, musculoskeletal conditions, neurological conditions, and COVID-19.
- The FDA has approved 29 products—10 of those between 2017 and 2021—with several more in the pipeline.
- There have been 180 requests for the Regenerative Medicine Advanced Therapy (RMAT) designation, the new accelerated approval pathway authorized under the 21st Century Cures Act, and 67 of those requests have been granted.

Still, more can be done. Ninety-five percent of active clinical trials in the United States are Phase 1 or Phase 2 trials. Many have promising results, but large-scale, randomized, placebo-controlled trials are needed to confirm the results of these early-stage trials. The greatest barrier to conducting these studies is the high cost of conducting them, particularly among academic and research institutions, as well as small biotechnology companies, who are responsible for the vast majority of clinical trials being conducted. Despite this financial barrier, only 17 percent of clinical studies have received any federal funding.

The NIH Regenerative Medicine Innovation Project website, which summarizes both funding announcements and awards made under each announcement, for funds authorized under the 21st Century Cures Act, summarizes 20 awards totaling $7.4 million. The Alliance for Cell Therapy Now and the Alliance for Cell Therapy Foundation understand that an additional $12.2 million has been awarded or committed for research projects and an additional $3.1 million is committed to a pending clinical trial award. Seventy-five percent of the awards posted on the NIH website supported pre-clinical research, as opposed to clinical trials.

Matching requirements contained in the 21st Century Cures Act provisions have been a barrier to promising research applicants and will become more of an issue with later stage, more costly trials.

The lack of federal funding for clinical trials, combined with existing matching requirements, serve as key barriers to bringing therapies to patients in need.

Additional resources are needed at the FDA to support this growing field.

Executive Summary

The FDA-related provisions from the 21st Century Cures Act have largely been implemented successfully, but additional resources are needed to support this growing field. Establishment of the Regenerative Medicine Advanced Therapies (RMAT) program is helping organizations seeking regulatory approval. However, the percentage of RMAT designation requests that have been granted has been declining over the last three years—from 46% in fiscal year 2019 to 28% in fiscal year 2022 to date.

Additional resources are needed at the FDA to support academic and research institutions, as well as small biotechnology companies, through educational sessions, workshops, and technical assistance, as they pursue regulatory approval in this emerging, promising field. In addition, resources are needed at the FDA to increase enforcement against clinics and other manufacturers who are not in compliance with relevant regenerative medicine regulations. Rogue actors continue to undermine legitimate scientific researchers and confuse patients in need of treatments for serious and life-threatening conditions.

This report describes these issues in further detail, and makes the following recommendations:

Recommendations for Advancing the Field

1. **Increase Federal Funding of Clinical Trials.** Significantly expand the level of investment in large-scale, randomized, placebo-controlled clinical trials exploring the use of regenerative medicine and cell and tissue-based therapies for serious and life-threatening conditions.
2. **Promote Collaboration on Evidence Development and Expand Cell Characterization.** The federal government should take actions to promote collaboration on evidence development, including funding support and incentives for collection of data on outcomes, as well as increased cell characterization, to improve evidence development and further increase understanding of the correlation of different products with clinical outcomes.
3. **Support Optimization and Scaling of Manufacturing.** Achieving the goal of scalable, cost-effective, high-quality therapies involving human cells will require federal support, given the complexity of biomanufacturing. This should take the form of direct funding, as well as incentives to manufacturers to invest in these activities.
4. **Increase Workforce Development Activities.** To address the needs of this growing field, the federal government should expand workforce development activities, including those within technical and community colleges, to build capacity and support the development of a skilled, technical workforce.
5. **Increase Capacity at the FDA.** Additional resources should be provided to the Center for Biologics Evaluation and Research to respond to and provide increased support to applicants seeking regulatory approval and to increase enforcement against clinics and others who are not in compliance with relevant regulations.

Congress and the Administration should build upon the leadership and support of regenerative medicine demonstrated through the passage and implementation of the bipartisan 21st Century Cures Act, to take the necessary steps to bring promising, safe, and effective regenerative medicine and cell and tissue-based therapies to patients in need.

The Alliance for Cell Therapy Now and the Alliance for Cell Therapy Foundation stand ready to assist policymakers as they consider and advance these and other strategies to advance the field.

Introduction

The 21st Century Cures Act contained clinical research and regulatory provisions designed to advance regenerative medicine and cell therapies

Regenerative medicine, including cell and tissue-based therapies (RMCTs), hold great promise for patients with serious and life-threatening conditions. As of December 31, 2021, there are more than 900 active clinical studies in the United States exploring the use of these therapies for a range of conditions, including cancer, cardiovascular disease, diabetes, eye-related conditions, musculoskeletal conditions, neurological conditions, and even COVID-19.

Five years ago, in December 2016, through a landmark, bipartisan effort, Congress passed—nearly unanimously—the 21st Century Cures Act (P.L. 116-255) (Cures Act) to accelerate biomedical research and bring new therapies to patients. The law included historic investments in research at the National Institutes of Health (NIH) and new authorities for the Food and Drug Administration (FDA).

The 21st Century Cures Act included several provisions—outlined below—related to RMCTs—to help bring safe and effective treatments and cures to patients to need.

Figure 1. 21st Century Cures Act Regenerative Medicine Provisions

- **Clinical Research.** Grants and contracts for clinical research totaling $30 million from the NIH to further the field of regenerative medicine using adult stem cells.
- **Regenerative Medicine Regulatory Framework.** Establishment of a program for the expedited review of certain regenerative advanced therapies by the FDA.
- **Annual Report.** Development and submission of an annual report to Congress on the number and types of applications to the FDA for approval and their status, as well as how many were granted accelerated approval or priority review.
- **Guidance Regarding Devices.** Development of FDA guidance clarifying regulatory evaluation of devices used in the recovery, isolation, or delivery of regenerative advanced therapies.
- **Standards for Regenerative Medicine.** Facilitation of an effort to coordinate and prioritze the development of standards.

In the five years since the passage of the 21st Century Cures Act, significant progress has been made by federal agencies—particularly the FDA—in carrying out many of the Cures Act provisions. However, more work is needed—in particular—to both fund and advance clinical research related to RMCTs, as well as scale and optimize manufacturing.

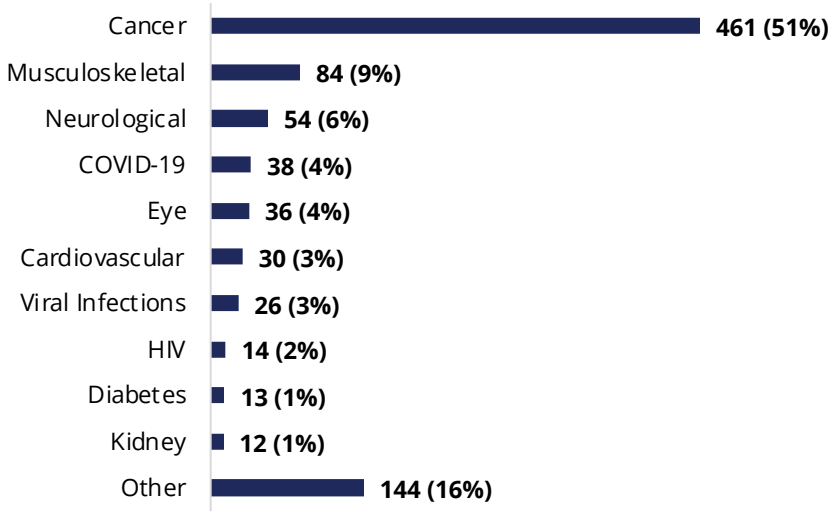
To this end, this report provides an examination of the current state of the field, an overview of the provisions contained in the 21st Century Cures Act, an analysis of federal agency implementation of such provisions in the five years since the Cures Act was passed and signed into law, and finally, recommendations for continuing to advance safe and effective RMCTs for patients in need.

Current State of the Field: Clinical Research

Since the passage of the 21st Century Cures Act five years ago, researchers in the United States and across the globe have accelerated their work to develop safe and effective cell-based therapies to help patients suffering from a range of conditions.

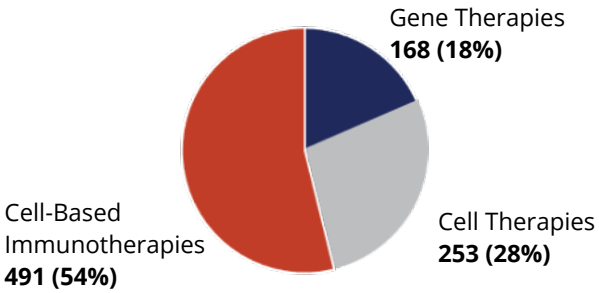
As of December 31, 2021, there are more than 900 active clinical studies in the U.S. that are exploring the use of these therapies for patients who suffer from a range of serious and life-threatening conditions. As summarized in Figure 2, cancer is the most prevalent condition being studied, representing 51% of all active clinical studies, followed by musculoskeletal conditions (9%), neurological conditions (6%), COVID-19 (4%), and eye-related conditions (4%).

Figure 2. Active U.S. Clinical Studies by Condition (n=912)



Most active U.S. clinical studies are exploring the use of cell-based immunotherapies (54%), followed by cell therapies (28%), and gene therapies (18%).

Figure 3. Active U.S. Clinical Studies by Product Type (n=912)

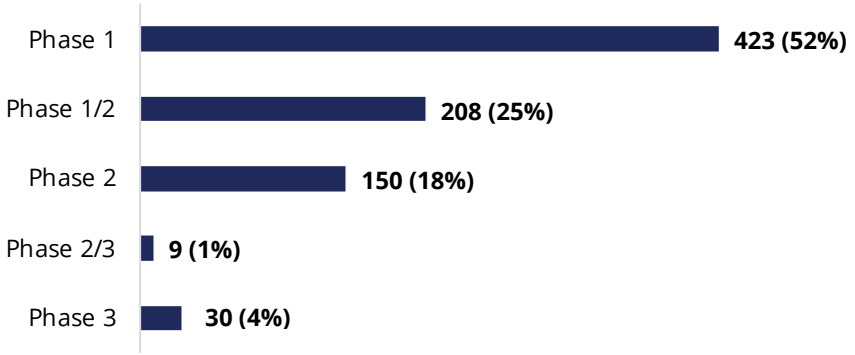


T-cells and T-Reg cells make up the majority (431 or 88%) of the 491 cell-based immunotherapies being explored, while the remainder (60 or 12%) are natural killer cells. Most of the 253 active clinical studies related to cell therapies are focused on MSCs (151 or 60%), followed by bone marrow aspirate concentrate (28 or 11%), stromal vascular fraction (SVF) (28 or 11%), induced pluripotent stem cells (iPSCs) (11 or 4%), and other cell therapies (35 or 14%).

Current State of the Field: Clinical Research

As summarized in Figure 4, the vast majority (95%) of the 820 active clinical trials exploring the use of cell therapies in the U.S., are either Phase 1 or Phase 2 trials.

Figure 4. Active U.S. Clinical Trials by Phase (n=820)



The vast majority—95%—of clinical trials are Phase 1 or Phase 2—large-scale, randomized, controlled trials are needed to confirm early results.

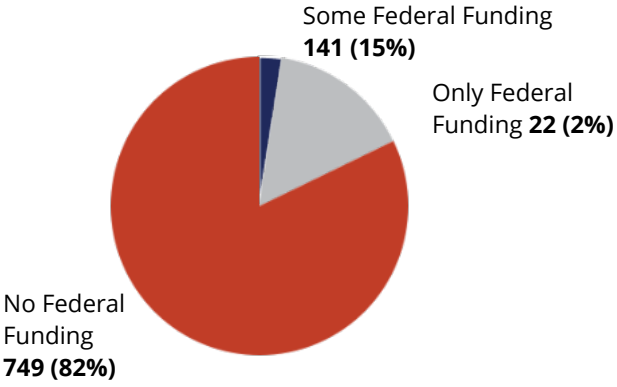
The largest barrier to conducting clinical trials is the lack of funding—only 17% of clinical studies have some level of funding support.

While the results from early phase clinical trials are promising, large-scale, randomized, placebo-controlled clinical trials are needed to confirm early results and help bring safe and effective therapies to patients in need.

The largest barrier to conducting clinical trials related to cell-based therapies is the high cost of conducting these studies. The financial barriers associated with clinical trials are particularly problematic for academic and research institutions as well as small biotechnology companies, who are responsible for most of the clinical trials being conducted both in the U.S. and abroad.

As noted in Figure 5 below, only 17% of active U.S. clinical studies have federal support.

Figure 5. Active U.S. Studies by Funding Source (n=912)



Current State of the Field: Product Approvals

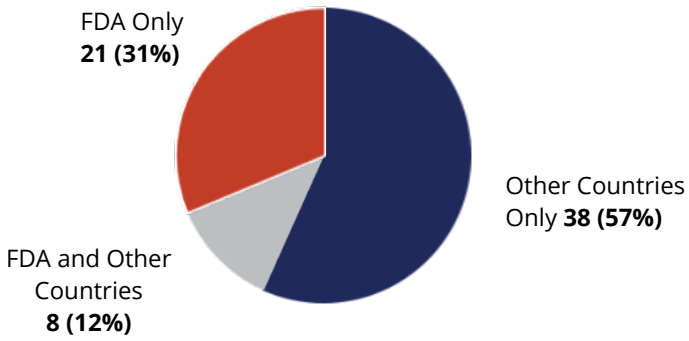
Currently, 67 regenerative medicine products are approved for use in various countries across the globe. The list—drawn from the webpage containing FDA-approved cellular and gene therapy products, FDA reports of approved medical devices, available products compiled by the Alliance for Regenerative Medicine, and individual product websites—includes cell-based immunotherapies, cell therapies, cord blood products, gene therapies, and tissue-engineered products. A comprehensive, detailed list of all approved products can be found in the Appendix.

Of the 67 products, 29 (or 43%) have been approved by the FDA, either as a licensed biologic (22) or a medical device (7). Forty-seven products have been approved by other internationally recognized regulatory agencies, including the EU's European Medicines Agency (20), Japan's Pharmaceuticals and Medical Devices Agency (9), South Korea's Ministry of Food and Drug Safety (15), and Health Canada (7), as well as other countries (10). An overview of products approved both within the U.S. and other countries is provided in Figure 6 below.

67 products have been approved world-wide, 29 (43%) in the U.S.

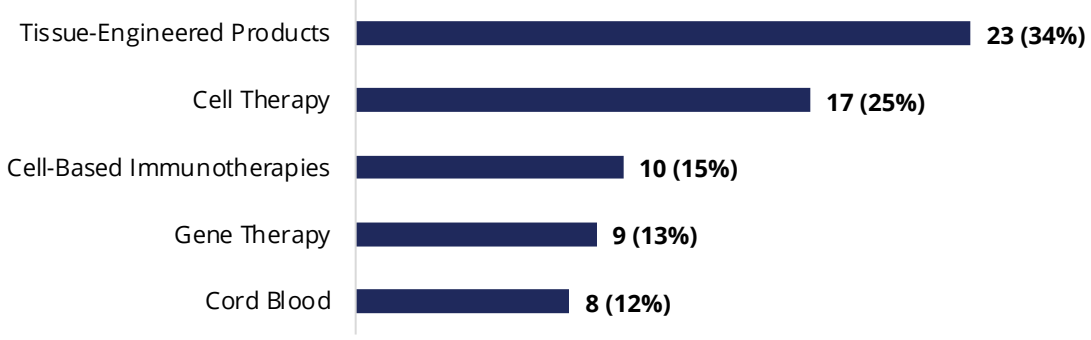
Tissue-engineered products and cell therapies make up nearly 60% of products approved globally.

Figure 6. Global Distribution of Approved Products (n=67)



As noted in Figure 7, tissue-engineered products (34%) and cell therapies (25%) make up nearly 60% of products approved across the globe, followed by cell-based immunotherapies (15%), gene therapies (13%), and cord blood products (12%). A majority (9 or 53%) of the 17 cell therapies approved globally are MSCs. Fibroblasts (3), keratinocytes (3), chondrocytes (1), and limbal stem cells (1), make up the remainder.

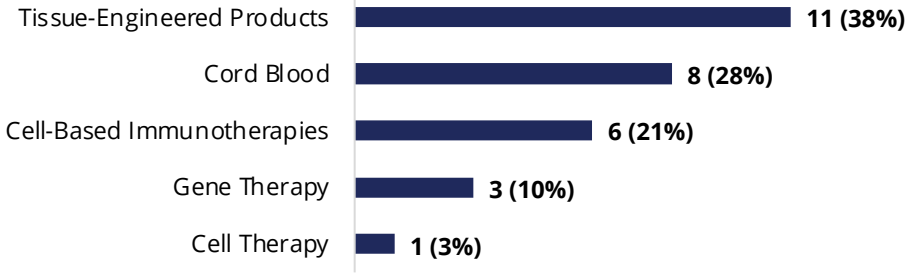
Figure 7. Product Approvals by Product Type (n=67)



Current State of the Field: Clinical Research

As noted in Figure 8, tissue-engineered products (38%), cord blood products (28%), and cell-based immunotherapies (21%) make up the majority of FDA approvals, followed by gene therapies (10%). Only one of the 29 products approved by FDA is a cell therapy.

Figure 8. FDA Approved Products, by Product Type (n=29)

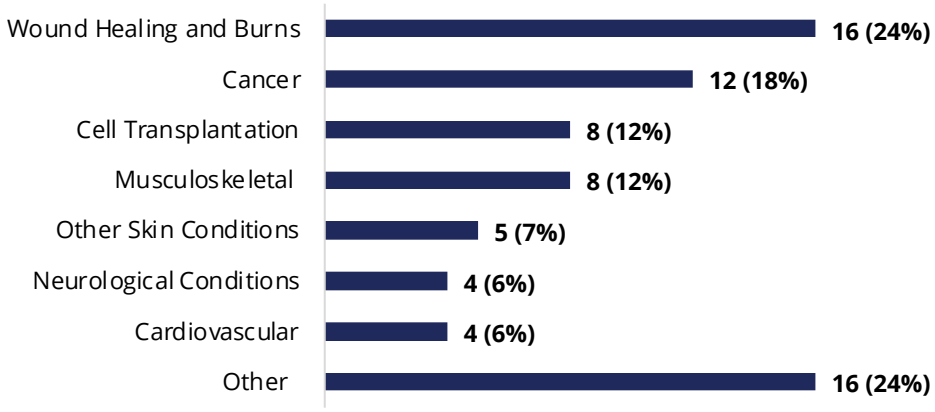


As highlighted in Figure 9, most approved products are focused on wound healing and burns (24%), cancer (18%), cell transplantation (12%), musculoskeletal conditions (12%), and other skin conditions (7%). Products focused on cardiovascular (6%) and neurodegenerative (6%) conditions have also been approved.

Tissue-engineered products, cord blood products, and cell-based immunotherapies make up the majority of FDA approvals.

FDA has approved only one cell therapy.

Figure 9. Products Approved by Condition (n=67)

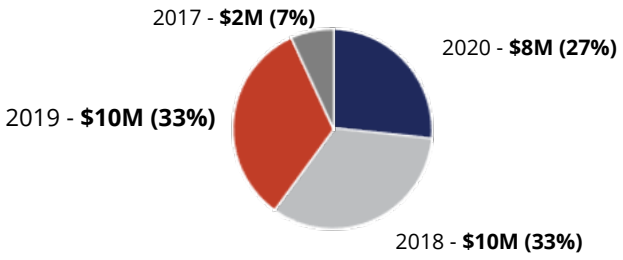


Note that percentages do not add up to 100% as some products are approved for multiple conditions.

Regenerative Medicine Clinical Research Provisions

Within Section 1001 of the 21st Century Cures Act, entitled Beau Biden Cancer Moonshot and NIH Innovation Projects, Congress called "for the NIH, in coordination with the FDA, to award grants and contracts for clinical research to further the field of regenerative medicine using adult stem cells, including autologous stem cells." Funding for this provision totaled $30 million, spanning fiscal years (FY) 2017 through 2020, as outlined in Figure 10. Congress further specified that matching funds be required from recipients of clinical research funding under the Act. A detailed analysis of federal agency implementation of these provisions, based on publicly available information, is summarized below.

Figure 10. Clinical Research Funding Authorized by 21st Century Cures Act



Within the 21st Century Cures Act, Congress authorized $30 million for clinical research grants and contracts to further the field of regenerative medicine.

Establishment of Regenerative Medicine Innovation Project

Following passage of the 21st Century Cures Act, NIH launched the Regenerative Medicine Innovation Project (RMIP), the purpose of which—according to the NIH RMIP project website—is "to accelerate progress in the field by supporting clinical research on adult stem cells, while promoting scientific rigor and protecting patient safety."

Clinical Research Funding Under Regenerative Medicine Innovation Project

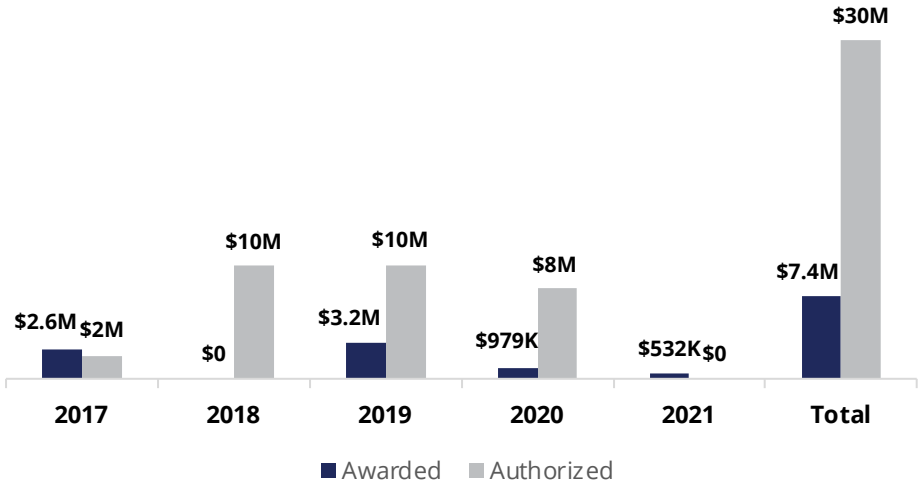
In response to the clinical research provisions contained in the 21st Century Cures Act, NIH published five funding opportunities, through the Regenerative Medicine Innovation Project, in 2017, 2018, 2019, 2020, and 2021. NIH then made awards corresponding to each funding opportunity, publicizing such awards on its NIH RMIP Funded Awards website.

A summary of the total funding for awards listed on the NIH RMIP Funded Awards website, as compared to amounts authorized by Congress, by year, is provided in Figure 11. According to the NIH RMIP Funded Awards website, and as outlined in Figure 11, NIH has publicly posted 20 awards totaling $7.4 million. The Alliance understands that an additional $12.2 million has been awarded or committed for research projects and an additional $3.1 million is committed to a pending clinical trial award.

Regenerative Medicine Clinical Research Provisions

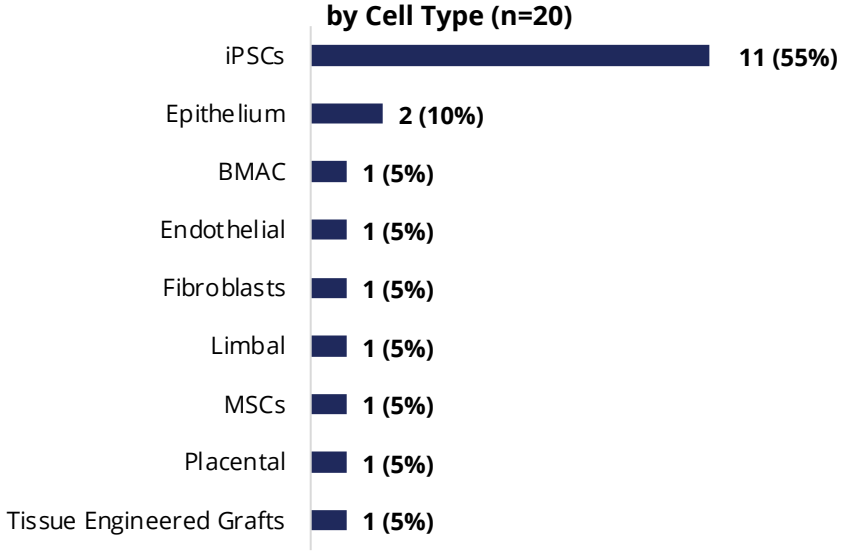
20 awards totaling $7.4 million have been posted on the NIH Regenerative Medicine Innovation Project website.

Figure 11. Clinical Research Funds Awarded vs. Authorized in 21st Century Cures



As shown in Figure 12, a majority—11 or 55%—of the awards made by NIH supported clinical research associated with iPSCs. Two of the awards supported research related to epithelium cells. The remaining 7 awards supported clinical research related to 7 different types of cells, including BMAC, endothelial cells, fibroblasts, limbal stem cells, MSCs, placental cells, and tissue-engineered grafts.

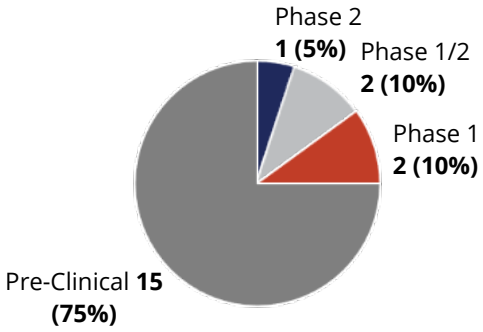
Figure 12. NIH Regenerative Medicine Innovation Awards by Cell Type (n=20)



Regenerative Medicine Clinical Research Provisions

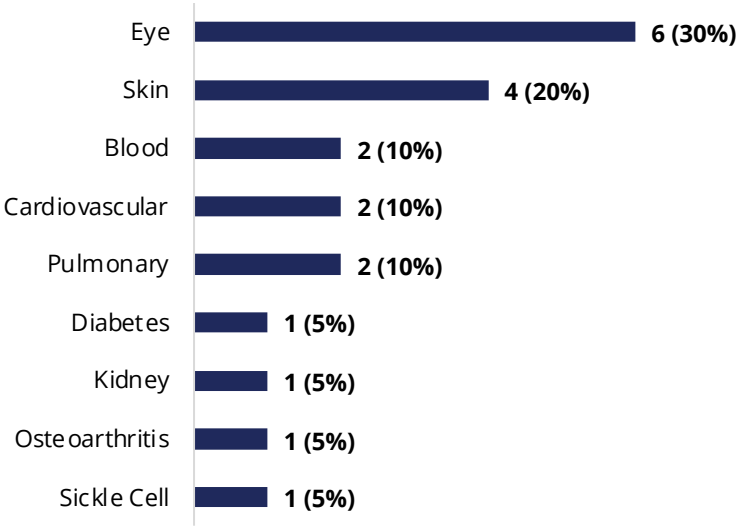
As summarized in Figure 13, 15 (or 75%) of the awards issued by NIH for clinical research supported pre-clinical studies, while the remaining five awards supported Phase 1 (2 awards), Phase 1/2 (2 awards), and Phase 2 studies (one award).

Figure 13. NIH Regenerative Medicine Innovation Awards by Phase (n=20)



Clinical research funded through the NIH Regenerative Medicine Innovation Project has focused on exploring the use of RMCTs for conditions such as corneal and other eye diseases (30%), skin conditions (20%), blood-related conditions (10%), cardiovascular disease (10%), pulmonary conditions (10%), and other conditions. An overview of the conditions addressed by NIH awards is provided in Figure 14.

Figure 14. NIH Regenerative Medicine Innovation Awards by Condition (n=20)



The majority of awards made public by the NIH—75%—were for pre-clinical studies.

Regenerative Medicine Clinical Research Provisions

Given the large gap between the $30 million in clinical research funding authorized by Congress and the total amount of awards ($7.4 million) listed on the NIH RMIP Funded Awards website, the Alliance reached out to NIH, followed by Congressional offices, to determine whether there may have been additional NIH awards made that were not reflected on the NIH website. Alliance staff were told that NIH had awarded or made commitments for an additional $12.2 million for research projects and an in-depth cell characterization hub—that are not reflected on the NIH RMIP website—and that NIH plans to spend an additional $3.1 million on a pending clinical trial award.

Regenerative Medicine Workshop

Approximately one year after the Act was passed and signed into law—in December 2017—NIH and FDA hosted a workshop, the purpose of which was to "identify critical gaps that must be addressed to enable significant innovation and rapid advancement of regenerative medicine approaches and explore issues related to product development and standards, regulatory science, and clinical applications." Key challenges identified by the workshop are summarized in Figure 15 below.

Figure 15. Key Challenges Identified in December 2017 Workshop

- Limited understanding of the identity and nature of stem cell products used in clinical applications.
- Need for effective methods for tracking and monitoring stem cell products in vivo.
- Need for regulatory "coaching" support to enable submission of well-supported IND/IDE applications.
- Difficulties in obtaining assistance with preparation of current Good Manufacturing Practice (cGMP)-compliant stem cell products.
- Need for improved data sharing.
- Importance of forging key regenerative medicine partnerships and collaborations.

Many of these—and other—challenges remain, including the need for federal support for optimization and scaling of manufacturing of regenerative medicine, including cell and tissue-based therapies, the need for increased resources for cell characterization, and the need for technical assistance to support navigation of regulatory requirements.

Regenerative Medicine Innovation Catalyst

In addition to hosting the December 2017 workshop and providing awards for clinical research, NIH established the Regenerative Medicine Innovation Catalyst (RMIC) to conduct in-depth characterization of the source of stem cells and stem cell-derived products to be administered to research subjects, as well as provide storage and dissemination services for in-depth cell characterization results and clinical data. Researchers funded through the NIH RMIP—such as the 20 awardees described previously—are expected to provide representative samples of the source stem cells and clinical-grade stem cell products for in-depth characterization through the RMIC. The RMIC is expected to also provide a platform for sharing and analysis of clinical trial data and cell product characterization data, thereby potentially enabling correlation of stem cell attributes with clinical outcomes. Recent information about the progress of the Regenerative Medicine Catalyst is not readily available.

Regenerative Medicine Regulatory Provisions

The 21st Century Cures Act contained four provisions related to regenerative medicine and cell therapies that pertain to the FDA, including (1) development of a new regenerative medicine advanced therapies designation to support accelerated approval, (2) requirements for annual reporting to Congress, (3) development of guidance clarifying evaluation of devices used with regenerative advanced therapies, and (4) coordination and prioritization of related standards development. A more detailed summary of those provisions, along with an analysis of implementation based on publicly available information, is summarized below.

Regenerative Medicine Advanced Therapies Designation

Section 3033 of the 21st Century Cures Act called for the FDA to facilitate an efficient development program for, and expedite review of, regenerative advanced therapies.

In response to the 21st Century Cures Act, the FDA established the Regenerative Medicine Advanced Therapy (RMAT) program shortly after the Cures Act was signed into law in December 2016. Under the law, FDA must determine whether a therapy meets the established criteria related to RMAT designation within 60 days and provide a written description of the rationale for denial of any RMAT designation request. Sponsors of RMAT designated products are eligible for actions to expedite development and review, including early interactions with FDA to discuss any potential surrogate or intermediate endpoints to be used to support accelerated approval.

The Cures Act defined regenerative advanced therapies to include "cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act and part 1271 of title 21, Code of Federal Regulations… [that] treat, modify, reverse, or cure a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition."

Regenerative advanced therapies are eligible for several FDA expedited programs, including fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation, as well as RMAT designation. In February 2019, FDA published final guidance, Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, including policies related to the RMAT program.

This guidance is one of four guidance documents—outlined in Figure 16 below—that comprise FDA's comprehensive Framework for the Regulation of Regenerative Medicine Products, which together address how FDA plans to support and expedite the development of regenerative medicine products.

Figure 16. Four Guidances Contained in FDA Regulatory Framework for Regenerative Medicine

1. Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use, draft published in November 2017 and corrected in December 2017 and final published in July 2020.
2. Same Surgical Procedure Exception: Questions and Answers Regarding the Scope of the Exception, draft published in October 2014 and final published in November 2017.
3. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, draft published in November 2017 and final published in February 2019.
4. Evaluation of Devices Used with Regenerative Medicine Advanced Therapies, draft published in November 2017 and final published in February 2019.

Regenerative Medicine Regulatory Provisions

FDA also launched technical assistance programs to help product developers come into compliance.

A recent increase in the number of clinics offering therapies outside of clinical trials with unproven claims of safety and efficacy highlights the need for greater funding and resources for FDA CBER.

FDA has implemented several programs to provide technical assistance to those seeking guidance on regulation associated with regenerative advanced therapies, including the Tissue Reference Group Rapid Inquiry Program (TRIP). This program helps manufacturers, including those who market products to physicians or patients, obtain a rapid, preliminary, informal, non-binding assessment of how specific therapies are regulated. According to the FDA FY 2021 budget request, TRIP was intended to help product developers come into compliance with premarket approval requirements, advance an efficient path for safe and effective regenerative medicine products, and help foster beneficial new innovations. FDA also provides several different avenues—including through the RMAT Program, to obtain regulatory advice on their development programs. TRIP—which was intended to be a temporary program—ended on March 31, 2021.

FDA also created a special emergency program—Coronavirus Treatment Acceleration Program (CTAP)—for possible COVID-19 therapies, which uses every available method to move new treatments to patients as quickly as possible, while at the same time, finding out whether they are helpful or harmful. Given that more than 130 clinical studies have been launched to explore the use of cell-based therapies for patients with COVID-19—many with promising results—the program has been extremely helpful.

Unfortunately, advances in regenerative medicine and cell therapies have coincided with an increase in private clinics that market regenerative medicine therapies outside of clinical trials with unproven claims of safety and efficacy. Recent reports have shown an increase in unlicensed clinics operating outside of the law.

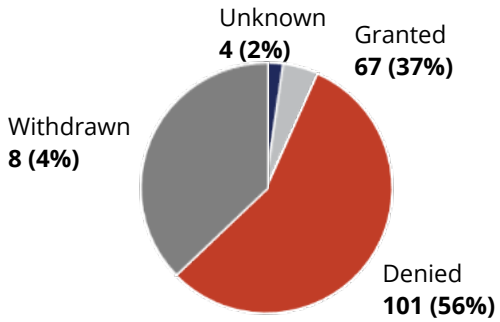
In response, as part of its regenerative medicine framework, FDA has taken regulatory and compliance action against a number of companies and individuals over the last several years for marketing products without FDA approval and for significant deviations from good manufacturing practice requirements—both of which put patients at risk, including issuance of hundreds of warning letters to stem cell marketers, clinics, and health care providers. The lack of resources within the FDA Center for Biologics Evaluation and Research (CBER)—combined with significant and necessary focus on evaluating potential COVID-19 vaccines and treatments—have likely contributed to FDA's inability to rapidly expand enforcement against unlicensed products.

Despite the increase in activity related to regenerative medicine and cell therapies, during the years subsequent to the passage of the 21st Century Cures Act, the number of FTEs within CBER has largely remained the same—averaging a little more than 1,400 during fiscal years 2017 through 2020.

Regenerative Medicine Regulatory Provisions

The implementation of the RMAT program as required by the 21st Century Cures Act spurred considerable interest and activity. As of December 31, 2021, FDA had received 180 requests for RMAT designation. As summarized in Figure 17, the majority of requests—56%—were denied. FDA granted RMAT designation to 67—or 37%—of those who made requests. Eight requests (or 4%) were withdrawn.

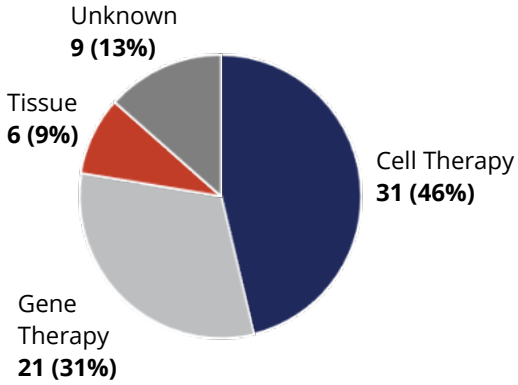
Figure 17. FDA RMAT Designation Decisions (n=180)



The percentage of RMAT designation requests that have been granted has been declining over the last three years—from 46% in fiscal year 2019 to 28% in fiscal year 2022 to date.

As highlighted in Figure 18, 31 (or 46%) of the 67 RMAT designations granted were for cell therapies—primarily cell-based immunotherapies. RMAT designations were granted to 21 gene therapy products, representing 31% of the total.

Figure 18. RMAT Designations by Product Type (n=67)



FDA has received 180 requests for RMAT designation, 37% of which have been granted and 56% of which have been denied.

Regenerative Medicine Regulatory Provisions

FDA carried out 21st Century Cures Act provisions related to annual reporting, device guidance, and standards.

Reporting to Congress

Section 3035 of the 21st Century Cures Act requires FDA to report to Congress on the number and types of applications for approval of regenerative advanced therapies that were filed, approved, licensed (as applicable), withdrawn, or denied, as well as how many were granted accelerated approval or priority review. There is no public reporting requirement in the law.

Guidance for Devices Used with Regenerative Medicine Advanced Therapies

Section 3034 of the 21st Century Cures Act requires the FDA to issue draft guidance—within one year—clarifying how it will evaluate devices used in the recovery, isolation, or delivery of regenerative advanced therapies. Such guidance is required to address the following:

- How the FDA intends to simplify and streamline regulatory requirements for combination products.
- Intended uses or specific attributes that would result in a device being classified as a Class III device.
- When the FDA considers it necessary—if ever—for the intended use to be specific to only one particular type of cell.
- Its application of the least burdensome approach to demonstrate how a device may be used for more than one cell type.

The Act further requires the FDA to publish final guidance within 12 months of the close of the public comment period. In compliance with the Act, the FDA issued draft guidance in November 2017, within one year of the Cures Act being passed and signed into law. The final guidance, Evaluation of Devices Used with Regenerative Medicine Advanced Therapies, was published in February 2019—within 12 months of the close of the comment period for the draft guidance in February 2018.

Standards for Regenerative Medicine

Section 3036 of the 21st Century Cures Act requires the FDA—within two years—in consultation with the National Institute of Standards and Technology (NIST) and stakeholders, to facilitate an effort to coordinate and prioritize the development of standards and consensus definition of terms, through a public process, to support the development, evaluation and review of regenerative advanced therapies, including with respect to the manufacturing processes and controls of such products.

In 2017, FDA awarded an annual contract to Nexight Group and the Standards Coordinating Body to coordinate community efforts toward the development of standards for regenerative medicine therapies. According to the FDA, under these contracts, Nexight has utilized public workshops and webinars to develop processes that have enabled the identification of needed standards and facilitated the development of standards that have a high impact on the quality and safety of regenerative medicine therapies.

In addition, Nexight has published "The Regenerative Medicine Standards Landscape," a report identifying needed standards, standards under development, and existing standards applicable to analytical testing, bioprocessing, product quality, preclinical study standards, and clinical trials of regenerative medicine therapies. To support sponsors seeking approval of their products, in March 2019, FDA issued guidance on the use of standards for regulatory submissions, Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research.

Recommendations

Early results from clinical trials and the growing number of product approvals show that regenerative medicine and cell therapies hold great promise for patients with serious and life-threatening conditions, including cancer, cardiovascular disease, diabetes, eye-related conditions, neurological and musculoskeletal conditions, wound healing, and more recently, COVID-19.

The vast majority—about 95%—of clinical trials are Phase 1 or Phase 2 trials. While the results from early phase clinical trials are promising, large-scale, randomized, placebo-controlled trials are needed to confirm early results and help bring safe and effective therapies to patients in need.

As noted in this report, the greatest barrier to conducting later stage trials is the high cost of conducting these studies, particularly among academic and research institutions and small biotechnology companies, who are responsible for most of the clinical trials being conducted both in the U.S. and abroad. Federal funding is urgently needed to help bring promising regenerative medicine and cell-based therapies to patients with serious and life-threatening conditions.

Congress' initial investment of $30 million in clinical research for regenerative medicine and cell therapies, along with other provisions contained in the 21st Century Cures Act, were unprecedented and very positive first steps toward advancing promising new therapies for patients. However, additional funding for clinical trials is needed to help realize the promise of these therapies.

Matching requirements contained in the 21st Century Cures provisions also served as a key barrier to promising researcher applicants and will become more of an issue in the case of funding support for later stage trials, which are more costly.

Congress and the Administration should build upon, but significantly expand, federal funding efforts focused on clinical research exploring the use of regenerative medicine, including cell and tissue-based therapies, for patients with serious and life-threatening conditions.

Policymakers should also provide greater funding support for cell characterization, as well as optimization and scaling of manufacturing of these therapies. It should also support a clinical trials network to further research collaboration and the sharing of best practices and lessons learned, as well as workforce development activities. These activities should involve frequent engagement of and collaboration with researchers, industry, and other stakeholders.

The FDA-related provisions from the 21st Century Cures Act have largely been implemented successfully, but FDA should increase the number of educational sessions and workshops, and provide greater technical assistance to academic and research institutions, as well as small biotechnology companies, who need support as they develop regenerative medicine therapies and prepare for FDA review.

Congress should consider additional funding support to FDA CBER so that the Center can increase its capacity to be able to effectively support this growing field. Additional FDA resources are also needed to increase enforcement against clinics and other manufacturers who are not in compliance with relevant regenerative medicine regulations. Rogue actors continue to undermine legitimate scientific researchers and confuse patients in need of treatments for serious and life-threatening conditions.

More federal funding is needed to support later stage clinical trials as well as optimization and scaling of manufacturing.

Recommendations

To provide leadership, coordinate, and carry out the activities described above, the Department of Health and Human Services (HHS) Secretary should establish a new program, focused on the study, development, and manufacturing of adult cell and tissue- based therapies, engaging the NIH, FDA, the Office of the Assistant Secretary for Preparedness and Response (ASPR), the Health Resources and Services Administration (HRSA), the Department of Defense, the Department of Veterans Affairs, and other federal agencies as appropriate.

A new advisory committee should be established—comprised of outside experts, including academic researchers with experience conducting studies using adult cell and tissue-based therapies, industry researchers and manufacturers working in the field of regenerative medicine and cell and tissue-based therapies, and patients—to provide guidance to the program.

In summary, as outlined in Figure 19, Congress and the Administration should take the following actions to fully realize the promise of regenerative medicine and cell-based therapies:

Recommendations for Advancing the Field

1. **Increase Federal Funding of Clinical Trials.** Significantly expand the level of investment in large-scale, randomized, placebo-controlled clinical trials exploring the use of regenerative medicine and cell and tissue-based therapies for serious and life-threatening conditions.
2. **Promote Collaboration on Evidence Development and Expand Cell Characterization.** The federal government should take actions to promote collaboration on evidence development, including funding support and incentives for collection of data on outcomes, as well as increased cell characterization, to improve evidence development and further increase understanding of the correlation of different products with clinical outcomes.
3. **Support Optimization and Scaling of Manufacturing.** Achieving the goal of scalable, cost-effective, high-quality therapies involving human cells will require federal support, given the complexity of biomanufacturing. This should take the form of direct funding, as well as incentives to manufacturers to invest in these activities.
4. **Increase Workforce Development Activities.** To address the needs of this growing field, the federal government should expand workforce development activities, including those within technical and community colleges, to build capacity and support the development of a skilled, technical workforce.
5. **Increase Capacity at the FDA.** Additional resources should be provided to the Center for Biologics Evaluation and Research to respond to and provide increased support to applicants seeking regulatory approval and to increase enforcement against clinics and others who are not in compliance with relevant regulations.

Congress has already demonstrated bipartisan support for regenerative medicine and cell therapies through passage of provisions within the 21st Century Cures Act. Language related to regenerative medicine and cell therapies has also been included in authorizing and appropriations legislation introduced and passed since the 21st Century Cures Act became law.

In the coming year, Congress should build upon this support by advancing legislation that will address the goals outlined above, which will help bring promising, safe, and effective regenerative medicine and cell therapies to patients in need.

Appendix: List of Approved Products

The following is a summary of details associated with products approved for use in the United States and abroad, categorized by product type. Information contained in this chart was drawn from approved products contained on the FDA list of approved cellular and gene therapy products, various FDA approval pages related to medical devices, the list of "Available Products" compiled by the Alliance for Regenerative Medicine, and individual product websites.

Product Name	Sponsor	Product Type	Indication	FDA Approval	FDA Approval Type	Global Approval	Country
ABECMA	Bristol-Myers Squibb	Cell-Based Immuno-therapy	Cancer	Yes	Biologic	Yes	Canada Europe
ALLOCORD	SSM Cardinal Glennon Children's Medical Center	Cord Blood	Cell Trans-plantation	Yes	Biologic		
ALOFISEL	Tigenix	Cell Therapy	Crohn's Fistula	No		Yes	Europe
APCEDEN	APAC Biotech	Cell-Based Immuno-therapy	Cancer	No		Yes	India
APLIGRAF	Organo-genesis, Novartis	Tissue-Engineered Product	Wounds – Leg, Foot Ulcers	Yes	Device		
AURIX	Nuo Therapeutics	Tissue-Engineered Product	Wounds	Yes	Device		
BREYANZI	Juno Therapeutics, a Bristol-Myers Squibb Company	Cell-Based Immuno-therapy	Cancer	Yes	Biologic		
CARDIOCEL	Admedus	Tissue-Engineered Product	Cardio-vascular	Yes	Device	Yes	Canada Europe Singapore
CARTEYVA	JW Therapeutics	Cell-Based Immuno-therapy	Cancer	No		Yes	China
CARTISTEM	Medipost	Cell Therapy	Knee Cartilage Defects	No		Yes	S. Korea
CELLGRAM-AMI	FCB Pharmicell	Cell Therapy	Cardio-vascular	No		Yes	S. Korea
CLEVECORD	Cleveland Cord Blood Center	Cord Blood Product		Yes	Biologic		
COLLATE-GENE	Anges	Gene Therapy	Critical Limb Ischemia	No		Yes	Japan

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Product Name	Sponsor	Product Type	Indication	FDA Approval	FDA Approval Type	Global Approval	Country
CREAVAX RCC	JW Creagene	Cell-Based Immuno-therapy	Cancer	No		Yes	S. Korea
CUPISTEM	Anterogen	Cell Therapy	Crohn's Fistula	No		Yes	S. Korea
CURESKIN	S. Biomedics	Cell Therapy	Acne Scars	No		Yes	S. Korea
DERMA-GRAFT	Organo-genesis, Inc.	Tissue-Engineered Product	Wound, Foot Ulcers	Yes	Device		
DUCORD	Duke University School of Medicine	Cord Blood Product	Cell Trans-plantation	Yes	Biologic		
EPICEL	Vericel	Tissue-Engineered Product	Wounds -Burns	Yes	Device		
GENDICINE	Shenzen Sibiono Genetech	Gene Therapy	Cancer	No		Yes	China
GINTUIT	Organo-genesis, Inc.	Tissue-Engineered Product	Wounds - Gingiva	Yes	Biologic		
HEART SHEET	Terumo BCT	Tissue-Engineered Product	Cardio-vascular Wounds - Burns	No		Yes	Japan
HEMACORD	New York Blood Center	Cord Blood Product	Cell Trans-plantation	Yes	Biologic		
HOLLODERM	Tego Science	Tissue-Engineered Product	Wounds – Burns, Other	No		Yes	S. Korea
HOLOCLAR	Chiesi Farmaceutici	Cell Therapy	Eye-Related Conditions	No		Yes	Europe
HPC CORD BLOOD	Bloodworks	Cord Blood Product	Cell Trans-plantation	Yes	Biologic		
HPC CORD BLOOD	Clinimmune Labs, University of CO Cord Blood Bank	Cord Blood Product	Cell Trans-plantation	Yes	Biologic		
HPC CORD BLOOD	LifeSouth Community Blood Centers, Inc.	Cord Blood Product	Cell Trans-plantation	Yes	Biologic		

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Product Name	Sponsor	Product Type	Indication	FDA Approval	FDA Approval Type	Global Approval	Country
HPC CORD BLOOD	MD Anderson Cord Blood Bank	Cord Blood Product	Cell Trans-plantation	Yes	Biologic		
HYALOGRAFT 3D	CHA Bio & Diostech Co. Ltd.	Tissue-Engineered Product	Wounds – Foot Ulcers	No		Yes	S. Korea
IMLYGIC	BioVex, Inc., a subsidiary of Amgen Inc.	Gene Therapy	Cancer	Yes	Biologic	Yes	Australia Europe
IMMUNCELL-LC	GC Pharma	Cell-Based Immuno-therapy		No		Yes	S. Korea
JACC	J-TEC	Tissue-Engineered Product	Knee Cartilage Defects	No		Yes	Japan
JACE	J-TEC	Tissue-Engineered Product	Wounds - Burns	No		Yes	Japan
KALODERM	Tego Science	Cell Therapy	Wounds – Burns, Ulcers	No		Yes	S. Korea
KERAHEAL	BioSolutions	Cell Therapy	Wounds - Burns	No		Yes	S. Korea
KERAHEAL-ALLO	BioSolutions	Cell Therapy	Wounds - Burns	No		Yes	S. Korea
KYMRIAH	Novartis Pharma-ceutical Corporation	Cell-Based Immuno-therapy	Cancer	Yes	Biologic	Yes	Canada Europe Japan Singapore
LAVIV	Fibrocell Technologies	Cell Therapy	Nasolabial Fold Wrinkles	Yes	Biologic		
LIBMELDY	Orchard Therapeutics	Gene Therapy	Meta-chromatic Leuko-dystrophy			Yes	Europe
LUXTURNA	Spark Therapeutics, Inc.	Gene Therapy	Eye-Related Conditions	Yes	Biologic	Yes	Canada Europe
MACI	Vericel Corp.	Tissue-Engineered Product	Knee Cartilage Defects	Yes	Biologic		
NEURO-NATA-R	Corestem	Cell Therapy	ALS	No		Yes	S. Korea
NOVOCART 3D	Aesculap Biologics	Tissue-Engineered Product	Articular Cartilage Repair	No		Yes	Europe

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Product Name	Sponsor	Product Type	Indication	FDA Approval	FDA Approval Type	Global Approval	Country
OMNIGRAFT	Integra	Tissue-Engineered Product	Wounds – Foot Ulcers	Yes	Device		
ORTHO-ACI	Orthocell	Tissue-Engineered Product	Articular Cartilage Repair	No		Yes	Australia
OSSRON	Sewon Cellontech	Tissue-Engineered Product	Bone Defects	No		Yes	India S. Korea
PROVENGE	Dendreon Corp.	Cell-Based Immuno-therapy	Cancer	Yes	Biologic		
QUEENCELL	Anterogen	Cell Therapy	Connective Tissue Disorders	No		Yes	S. Korea
REGENERCEL	Avita Medical	Tissue-Engineered Product	Wounds - Ulcers	No		Yes	Europe
RENOVACELL	Avita Medical	Tissue-Engineered Product	Skin Discoloration	No		Yes	Europe
RETHYMIC	Enzyvant Therapeutics GmbH	Tissue-Engineered Product	Congenital Athymia	Yes	Biologic		
ROSMIR	Tego Science	Cell Therapy	Under Eye Wrinkles	No		Yes	S. Korea
SKYSONA	bluebird bio, Inc.	Gene Therapy	Cerebral Adreno-leuko-dystrophy	No		Yes	Europe
SPHEROX	Co.Don. Ag	Cell Therapy	Cartilage Defects	No		Yes	Europe
STEMIRAC	Nipro Corp.	Cell Therapy	Spinal Cord Injury	No		Yes	Japan
STEMPEUCEL	Stempeutics Research Pvt	Cell Therapy	Critical Limb Ischemia	No		Yes	India
STRATA-GRAFT	Stratatech, a Mallinckrodt Company	Tissue-Engineered Product	Wounds - Burns	Yes	Biologic		

Appendix: List of Approved Products

Product Name	Sponsor	Product Type	Indication	FDA Approval	FDA Approval Type	Global Approval	Country
STRIMVELIS	Orchard Therapeutics, purchased from Glaxo-SmithKline	Gene Therapy	Severe Combined Immuno-deficiency, Adenosine Deaminase Deficiency (ADA-SKID)	No		Yes	Europe
TECARTUS	Kite Pharma, Inc. a Gilead Company	Cell-Based Immuno-therapy	Cancer	Yes	Biologic	Yes	Europe
TEMCELL	JCR Pharma-ceuticals Co Ltd, Licensee of Mesoblast	Cell Therapy	Cardiovascular COPD Crohn's Diabetes GVHD Radiation Injury	No		Yes	Canada Japan New Zealand
TRANSCYTE	Organo-genesis	Tissue-Engineered Product	Cerebral Adreno-leuko-dystrophy	Yes	Device	No	Europe
VERGENIX FG	Collplant	Tissue-Engineered Product	Epidermolysis Bullosa	No		Yes	Europe
VERGENIX STR	Collplant	Tissue-Engineered Product	Wounds	No		Yes	Europe
YESCARTA	Kite Pharma, Inc. a Gilead Company	Cell-Based Immuno-therapy	Cancer	Yes	Biologic	Yes	Canada China Europe Japan
ZOLGENSMA	Novartis Gene Therapies	Gene Therapy	Spinal Muscular Atrophy	Yes	Biologic	Yes	Canada Europe Japan
ZYNTEGLO	bluebird bio, Inc.	Gene Therapy	Beta-Thalassemia (Blood Disorder)	No		Yes	Europe

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About Alliance for Cell Therapy Now and Alliance for Cell Therapy Foundation

Alliance for Cell Therapy Now and the Alliance for Cell Therapy Foundation are independent, non-profit organizations guided by leaders representing academic and medical institutions, industry innovators, and patients, that are working to advance safe and effective regenerative medicine and cell therapies for patients in need. Visit http://allianceforcelltherapynow.org/

For More Information

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